

## PATENT COOPERATION TREATY

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(PCT Rule 61.2)

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Applicant's or agent's file reference  
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Priority date (day/month/year)  
13 May 1998 (13.05.98)

Applicant BROWN, Colin
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1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:  
10 December 1999 (10.12.99)

in a notice effecting later election filed with the International Bureau on:  
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2. The election  was  
 was not

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## PATENT COOPERATION TREATY

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NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
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11 August 2000 (11.08.00)

To:  
  
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Applicant's or agent's file reference  
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## IMPORTANT NOTIFICATION

International application No.  
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International filing date (day/month/year)  
13 May 1999 (13.05.99)

## 1. The following indications appeared on record concerning:

the applicant     the inventor     the agent     the common representative

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## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person     the name     the address     the nationality     the residence

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## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

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(54) Title: DEXTRIN-CONTAINING COMPOSITION FOR PREVENTING SURGICAL ADHESIONS

(57) Abstract

A method of preventing or reducing the incidence of post-operative adhesions in or associated with a body cavity, which comprises introducing into the body cavity a composition containing an aqueous solution or suspension or gel formulation containing the polysaccharide dextrin.

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## DEXTRIN-CONTAINING COMPOSITION FOR PREVENTING SURGICAL ADHESIONS

This invention relates to the prevention of surgical adhesions, and in particular to adhesions taking place in serous cavities including the peritoneum, the pericardium, 5 the plura and synovial cavities such as joints and tendons and to adhesions following spinal and/or cranial operations. Reference will be made hereinbelow to the prevention of adhesions in the peritoneum but it should be understood that the present invention has applicability in connection with other serous cavities in both humans and animals.

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Abdominal surgery is a rapidly changing field. Many forms of open surgery are being increasingly replaced by laparoscopic procedures. Although considerable immediate post-surgical benefits have been demonstrated to follow from laparoscopic surgery, the incidence of adhesions has not decreased. The severe 15 drying of the mesothelium which results from prolonged exposure of the peritoneum to dry gases (pneumoperitoneum of 2-4 hours), may give rise to a higher incidence of global peritoneal adhesions than has hitherto been encountered in open surgery. Many gynaecologists with long experience of laparoscopic surgery consider that both open and closed surgery have equally high incidences of adhesions.

20

WO 92/21354 describes a surgical adhesion as the attachment of organs or tissues to each other through scar tissue. A formation of scar tissue is described as a normal sequel to surgery or other tissue injury and is required for proper wound healing. In some cases, however, the scar tissue overgrows the intended region and creates 25 surgical adhesions. These scar tissue surgical adhesions restrict the normal mobility and function of affected body parts. The invention disclosed in WO 92/21354 is based on the discovery that anionic polymers effectively inhibit invasion of cells associated with detrimental healing processes, ie, fibrosis, and scaring. In particular, certain inhibitory anionic polymers are useful to inhibit fibroblast invasion, thus regulating the healing process and preventing fibrosis. Anionic polymers specified in 30 WO 92/21354 include dextran sulfate, pentosan polysulfate as well as natural

proteoglycans, or the glycosaminoglycan moieties of proteoglycans, including dermatan sulfate, chondroitin sulfate, keratan sulfate, heparan sulfate, heparin and alginate.

- 5 By attempting to inhibit fibroblast invasion, the approach of WO 92/21354 is one of post-adhesion treatment since fibroblast invasion is a later stage, that is to say, it occurs after formation of the adhesion. The invention of WO 92/21354 attempts to prevent the adhesion becoming permanent. By contrast the present invention is concerned with the prevention of the occurrence of an adhesion.

10

According to a first aspect of the present invention there is provided a method of preventing or reducing the incidence of post-operative adhesions in or associated with a body cavity, which comprises introducing into the body cavity an aqueous solution or suspension or gel formulation containing the polysaccharide dextrin.

15

The term "dextrin" means a glucose polymer which is produced by the hydrolysis of starch and which consists of glucose units linked together by means mainly of  $\alpha$ -1,4 linkages. Typically dextrans are produced by the hydrolysis of starch obtained from various natural products such as wheat, rice, maize and tapioca. In addition to  $\alpha$ -1,4 linkages, there may be a proportion of  $\alpha$ -1,6 linkages in a particular dextrin, the amount depending on the starch starting material. Since the rate of biodegradability of  $\alpha$ -1,6 linkages is typically less than that for  $\alpha$ -1,4 linkages, it is preferred that, for many applications, the percentage of  $\alpha$ -1,6 linkages is less than 10% and more preferably less than 5%.

25

Any dextrin is a mixture of polyglucose molecules of different chain lengths. As a result no single number can adequately characterise the molecular weight of such a polymer. Accordingly, various averages are used, the most common being the weight average molecular weight ( $M_w$ ) and the number average molecular weight ( $M_n$ ).  $M_w$  is particularly sensitive to changes in the high molecular weight content

of a polymer whilst Mn is largely influenced by changes in the low molecular weight content of the polymer.

It is preferred that the Mn of the dextrin is in the range of from 1,000 to 30,000 and  
5 ideally the Mw is in the range of from 3,000 to 50,000. More preferably, the Mn is from 3,000 to 8,000 and the Mw is from 5,000 to 50,000.

The term "degree of polymerisation" (DP) can also be used in connection with polymer mixtures. For a single polymer molecule, DP means the number of polymer  
10 units. For a mixture of molecules of different DP's, weight average DP and number average DP correspond to Mw and Mn. In addition, DP can also be used to characterise a polymer by referring to the polymer mixture having a certain percentage of polymers of DP greater than a particular number or less than a particular number.

15

It is preferred that the dextrin contains more than 15% of polymers of DP greater than 12 and, more preferably, more than 50% of polymers of DP greater than 12.

The dextrin used in the present invention is water soluble or at least forms a  
20 suspension in water or a gel formulation. The dextrin used in this invention may be in the form of either unsubstituted dextrin (as obtained by the hydrolysis of starch) or may be substituted by one or more different groups. The substituents may be negatively charged groups, for instance, sulfate groups, neutral groups, or positively charged groups, for instance, quaternary ammonium groups. In the case where the  
25 substituent group is sulfate, it is preferred that the sulfated polysaccharide contains at least one sulfate group per saccharide (glucose) unit.

The present invention also provides a composition comprising an aqueous solution or suspension or gel formulation of the polysaccharide dextrin in which the amount of  
30 dextrin is effective to prevent or reduce the incidence of post-operative adhesions.

The present invention further provides the use of a composition in the prevention or reduction of the incidence of post-operative adhesions, the composition comprising a aqueous solution or suspension or gel formulation of the polysaccharide dextrin.

5     The present invention further provides the use of the polysaccharide dextrin in the manufacture of a composition comprising an aqueous solution or suspension or gel formulation of dextrin for preventing or reducing post-operative adhesions in humans and animals.

10    Dextrin is a useful material for the production of an adhesion-preventing composition because, *inter alia*, it is non-toxic, cheap and has the ability to hold fluid in a body cavity. It is also readily metabolised within the body.

15    Preferably, a composition of the invention is applied to the appropriate body cavity or area after the operation has been carried out.

20    Preferably, the composition of the present invention is allowed to remain in the body cavity for a minimum of 2 to 3 days and especially over the period during which fibrin exudation is at a maximum. More preferably, the composition should remain in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).

25    Preferably, a composition of the invention should be applied to the body cavity in a volume large enough to keep the surfaces apart. For the peritoneum, the volume should preferably be in the range 500-2000 ml and, more preferably, about 1000 ml-1500 ml.

30    Preferably, the composition should be applied to the appropriate body cavity or area in differing concentrations ideally over a concentration range of 2.5-18% and more ideally over a concentration range of 3-5% and most ideally at about 4% by weight,

said concentration range is selected for a specified time span, even more ideally the concentration range is selectively altered over a period of time.

Preferably, the composition should include a concentration of dextrin which is such  
5 that the fluid largely holds in place over the period it resides in the cavity. Where a composition includes 4% by weight of dextrin then a suitable dwell period for one infusion might be of the order of 2 to 3 days. A high concentration is liable to cause ingress of fluid. A second infusion at day 3 may extend the total dwell period from 6 to 7 days.

10

Alternatively, a composition having a dextrin concentration of from 12 to 15% by weight may be used in a smaller volume (perhaps about 750 ml) and will be subject to ingress of fluid. However a single infusion might be sufficient for the full 6 to 7 day period.

15

Comparing dextrin with dextran, the latter has relatively poor biocompatibility. It is subject to immunological hypersensitivity due to its concentration in lymph nodes and its lack of metabolisability. At best, a dextran solution or suspension will act not so much to separate surfaces and therefore prevent adhesions but simply as a lubricant. Dextrin advantageously serves as an osmotic agent, which can maintain the volume of a solution in the peritoneal cavity. The continued presence of the dextrin solution within the cavity serves to separate tissues which otherwise may adhere to each other.

25 The use of a solution or suspension or gel formulation of dextrin is also advantageous by comparison with a prior art technique which makes use of synthetic films in the form of patches which are applied to particular areas where maximum damage has occurred. However, in the case of a body cavity, such as the peritoneum, the damage is liable to occur as well at a distance from the operative site, especially in  
30 laparoscopy, due to the drying which takes place. In some instances global damage over an area of as much as two square metres can take place.

In responding to a wound, the body causes circulating fibrinogen to form fibrin and it is this production of fibrin which is associated with the formation of adhesions. Calcium ions are required to polymerise fibrinogen to fibrin and, accordingly, a composition of the present invention may include a calcium binding agent such as  
5 EDTA or sodium citrate.

A composition of the present invention may include a suitable lubricant such as a phospholipid.

10 A composition of the present invention may include a hyaluronate or glycocosolaminoglycan, a material which is associated with serosal lubrication and which has strong anti-adhesive properties. In this case the dextrin solution or suspension or gel formulation is effective in spreading the hyaluronate throughout the whole peritoneum.

15 A composition of the present invention may include an antibiotic agent or a material/agent which is associated with preventing an infection or build up of bacteria or foreign bodies or the like. A composition including such a material/agent would be particularly advantageous in prevention or amelioration of pelvic  
20 inflammatory disease.

A composition of the present invention may also include a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate and/or methylene blue.

25 The present invention provides a preferred composition comprising an aqueous solution or suspension or gel formulation of dextrin, one or more phospholipids and hyaluronate. Such a composition is not only highly effective in preventing adhesions but also has a good shelf life.

30

Mesothelial secretion of prostacyclin has been demonstrated and this activity enhances the non-stick properties of the mesothelium. The present invention provides a composition comprising dextrin together with prostacyclin or an analogue thereof.

- 5 According to a second aspect of the invention there is provided a biocompatible, bioresorbable, and non-toxic post-operative adhesion prevention kit for surgical use in humans or animals, comprising an aqueous solution or suspension or gel formulation of dextrin as hereinbefore described, and optionally or additionally comprising a calcium binding agent as hereinbefore described and/or a suitable
- 10 lubricant as hereinbefore described and/or prostacyclin or an analogue thereof as hereinbefore described and/or an antibiotic agent as hereinbefore described..

#### EVIDENCE IN SUPPORT OF THE INVENTION

##### 15 PROTOCOL:

- Animals: One hundred thirty, female New Zealand White rabbits, 2.4-2.7 kg, were purchased from Irish Farms (Norco, CA) and quarantined in the USC Vivaria for at least 2 days prior to use. Ten rabbits were randomised into thirteen treatment groups prior to initiation of surgery. The rabbits were housed on a 12:12 light:dark cycle 20 with food and water available *ad libitum*.

- Materials: The solutions (7.5% [wt/vol] icodextrin-Lot # 98A06G33, 20% [wt/vol] icodextrin-Batch # SP184772 and placebo (electrolyte solution for icodextrin)-Batch # SP184829 were supplied by ML Laboratories Plc. Icodextrin is a [1 → 4] - α - 25 Glucan having more than 85% of its molecules with molecular weights between 1,640 - 45,000 with a weight average molecular weight of approximately 20,000. The placebo electrolyte solution contained 5.4g sodium chloride, 4.5g sodium lactate, 257 mg calcium chloride, 51 mg magnesium chloride in 1 litre water for injection. The sutures used to close the muscle and skin were 3-0 coated Dexon II suture (Davis 30 and Geck, Manati, PR).

Double Uterine Horn Model: Rabbits were anaesthetised with a mixture of 55 mg/kg ketamine hydrochloride and 5 mg/kg Rompum intramuscularly. Following preparation for sterile surgery, a midline laparotomy was performed. The uterine horns were exteriorised and traumatised by abrasion of the serosal surface with gauze until punctuate bleeding developed. Ischaemia of both uterine horns was induced by removal of the collateral blood supply. The remaining blood supply to the uterine horns was the ascending branches of the utero-vaginal arterial supply of the myometrium. At the end of surgery, 10 to 75 ml (10, 25, 50, 75 ml) of 7.5% or 20% icodextrin, 10 or 75 ml placebo or no treatment (control) was administered. After 7 days, the rabbits were terminated and the percentage of the area of the horns adherent to the various organs was determined. In addition, the tenacity of the adhesions was scored using the following system:

- 0 = No adhesions;  
15 1 = Mild, easily dissectable adhesions;  
2 = Moderate adhesions; non-dissectable, does not tear the organ;  
3 = Dense adhesions; non-dissectable, tears organ when removed.

In addition an overall score which takes into account all of the above data was given  
20 to each rabbit. The following scoring system was used:

- 0 = No adhesions;  
0.5+ = Light, filmy pelvic adhesions involving only one organ, typically only 1 or 2 small adhesions;  
25 1.0+ = Light, filmy adhesions, not extensive although slightly more extensive than 0.5;  
1.5+ = Adhesions slightly tougher and more extensive than a 1 rating;  
2.0+ = Tougher adhesions, a little more extensive, uterine horns usually have adhesions to both bowel and bladder;  
30 2.5+ = Same as 2, except the adhesions are usually not filmy at any site and more extensive;

- 3.0+ Tougher adhesions than 2, more extensive, both horns are attached to the bowel and bladder, some movement of the uterus possible;  
3.5+ Same as 3, but adhesions slightly more extensive and tougher;  
4.0+ Severe adhesions, both horns attached to the bowel and bladder,  
5 unable to move the uterus without tearing the adhesions.

The rabbits were scored by two independent observers that were blinded to the prior treatment of the animal. If there was disagreement as to the score to be assigned to an individual animal, the higher score was given.

10

Statistical Analysis: The tenacity and overall scores were analysed by rank order analysis and analysis of variance on the ranks. The percentage area of the horns involved to the various organs was compared by Student's t test. The data from the incidence of adhesion formation was analysed by Chi square analysis. The  
15 comparison with placebo shown on Table 14 was done between the 10 ml placebo group and data from animals which received 10-25 ml of icodextrin or between the 75 ml placebo group and data from animals which received 50 or 75 ml icodextrin.

RESULTS: One rabbit from the group treated with 50 ml 20% icodextrin died  
20 postoperatively without evidence of inflammation or oedema at necropsy and was replaced. During the postoperative evaluation of the rabbits, it was noted that several rabbits given the higher volumes of icodextrin had "bulging" abdomens for the first few postoperative days. This occurred in 3 rabbits which received 75 ml or 7.5% icodextrin and 8 rabbits which received 75 ml of 20% icodextrin. The bulging was  
25 observed for 24 hours in the rabbits which received 7.5% icodextrin and 48-72 hours in the rabbits which received 20% icodextrin. This bulging was not observed in the group of rabbits which received 75 ml of placebo. No excess fluid was observed in any icodextrin or placebo-treated rabbits at necropsy. One rabbit, which received 75 ml of 20% icodextrin, had a small amount of subcutaneous fluid at necropsy.

30

The effect of icodextrin on the formation of adhesions in this rabbit model can be found in Tables 1-13. The effect of icodextrin on the incidence of adhesions can be found in Table 14. For each site, the extent and tenacity (tenacity in parentheses) of the adhesions between the horn and that site were given. In the final row of each 5 column (with the exception of the column on the far right), the mean and standard error of the mean for the extent score for each site is given. In the final row of the final column, the mean and standard error of the mean of the ranks is given. If an extent or rank order was reduced compared to control ( $p \leq 0.05$ ), a \* is in the appropriate row. At higher volumes (25 to 75 ml) of icodextrin, there was a 10 significant reduction in the formation of adhesions. However, no difference between the 7.5% and 20% solutions was noted in this study. This efficacy is in the absence of inflammation noted with some materials implanted intraperitoneally.

In conclusion results demonstrated that high volumes of icodextrin (both 15 percentages) were highly efficacious in the reduction of adhesion formation in this model with efficacy noted after administration of 50 ml or 75 ml of icodextrin. The lower volumes of icodextrin have less effect and the placebo had no effect on adhesion formation. Thus we have demonstrated that the composition of the present invention is effective in reducing the incidence of post-operative adhesion formation.

### Amended Claims

1. A composition for preventing or reducing the incidence of adhesions in or associated with a body cavity comprising an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.  
10
2. A composition according to Claim 1 wherein the aqueous formulation is a solution.
3. A composition according to Claim 1 wherein the aqueous formulation is a gel.  
15
4. A composition according to any preceding claim wherein the percentage of  $\alpha$ -1,6 linkages in the dextrin is less than 10%.
- 20 5. A composition according to Claim 4 wherein the percentage of  $\alpha$ -1,6 linkages in the dextrin is less than 5%.
6. A composition according to any preceding claim wherein the number average molecular weight ( $M_n$ ) of the dextrin is in the range 1,000 to 30,000.  
25
7. A composition according to Claim 6 wherein the  $M_n$  of the dextrin is in the range 3,000 to 8,000.
8. A composition according to any preceding claim wherein the weight average molecular weight ( $M_w$ ) of dextrin is in the range 3,000 to 50,000.  
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9. A composition according to Claim 8 wherein the Mw of the dextrin is from 5,000 to 50,000.
10. A composition according to any of Claims 1-9 wherein the dextrin contains more than 50% of polymers with a degree of polymerisation (DP) greater than 12.
11. A composition according to any preceding claim wherein the dextrin is unsubstituted dextrin.
12. A composition according to any of Claims 1-10 wherein the dextrin is substituted by one or more different groups selected from the group consisting of negatively charged groups, sulfate groups, neutral groups, positively charged groups and quaternary ammonium groups.
13. A composition according to Claim 12 wherein the dextrin is sulfated dextrin containing at least one sulfate group per saccharide (glucose) unit.
14. A composition according to any preceding claim in which the dextrin is present in an amount of from 2.5-18 % by weight of the composition.
15. A composition according to Claim 14 in which the dextrin is present in an amount of from 3-5 % by weight of the composition.
- 25 16. A composition according to either of Claims 14 or 15 in which the dextrin is present in an amount of about 4 % by weight of the composition.
17. A composition according to any preceding claim which further includes a calcium binding agent.

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18. A composition according to Claim 17 wherein the calcium binding agent is either EDTA or sodium citrate.
19. A composition according to any preceding claim which further includes a  
5 suitable lubricant.
20. A composition according to Claim 19 wherein the lubricant is a phospholipid.
21. A composition according to any preceding claim which further includes a  
10 hyaluronate.
22. A composition according to any preceding claim which further includes a compound selected from one or more of the following compounds, glycosolaminoglycan, an antibiotic agent, prostacyclin or an analogue thereof, a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an  
15 analogue thereof, dextrin sulphate and/or methylene blue.
23. A method of preventing or reducing the incidence of adhesions in or associated with a body cavity, which comprises introducing into the body cavity an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce the incidence of such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate  
20 tissues which otherwise may adhere to each other.
24. A method according to Claim 23 wherein the aqueous formulation is a solution.
- 30 25. A method according to Claim 23 wherein the aqueous formulation is a gel.

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26. A method according to any of Claims 23-25 wherein said composition is applied to the appropriate body cavity after a surgical operation has been carried out.

5 27. A method according to any of Claims 23-26 wherein the composition is allowed to remain in the body cavity for a minimum of 2 to 3 days.

10 28. A method according to any of Claims 23-27 wherein the composition is allowed to remain in the body cavity over the period during which fibrin exudation is at a maximum.

15 29. A method according to any of Claims 23-28 wherein the composition remains in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).

30. A method according to any of Claims 23-29 wherein the composition is applied to the peritoneal cavity in a volume in the range 500-2000 ml.

20 31. A method according to Claim 30 wherein the composition is applied to the peritoneal cavity in a volume in the range 1000 ml-1500 ml.

32. A method according to any of Claims 23-31 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 2.5-18 % by weight of the composition.

25 33. A method according to Claim 32 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 3-5 % by weight of the composition.

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34. A method according to either Claims 32 or 33 wherein the dextrin is applied to the appropriate body cavity in an amount of about 4 % by weight of the composition.
- 5 35. A method according to any of Claims 23-34 wherein the concentration range of the dextrin is selectively altered over a period of time.
- 10 36. A biocompatible, bioresorbable, and non-toxic adhesion prevention kit for surgical use in humans or animals, comprising an aqueous formulation of dextrin.
37. A kit according to Claim 36 wherein the aqueous formulation is either a solution or a gel.
- 15 38. Use of a composition according to Claim 1 and optionally including any one or more of the features of Claims 2-22 for preventing or reducing the incidence of adhesions in or associated with a body cavity which comprises introducing into the body cavity an aqueous formulation containing the polysaccharide dextrin wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.
- 20
- 25 39. Products containing an aqueous formulation of the polysaccharide dextrin and any one or more of the features of Claims 17-22 as a combined preparation for use in preventing or reducing the incidence of adhesions in or associated with a body cavity wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.
- 30

p15375w0.amended claims

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Table 1. Data from Surgical control Rabbits  
% Horn Involved

Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
30(2)	30(2)	30(1)	40(1)	30(2)	30(2)	30(1)	40(1)	2.5+
30(1)	30(1)	50(2)	50(2)	30(1)	30(1)	30(1)	50(2)	2.5+
30(2)	30(1)	40(2)	40(2)	30(2)	30(2)	40(2)	40(2)	3.0+
40(1)	20(1)	50(2)	30(1)	40(1)	20(1)	30(1)	30(1)	3.0+
20(1)	30(1)	50(2)	40(2)	20(1)	30(1)	50(2)	40(2)	3.0+
40(1)	30(1)	50(1)	40(1)	40(1)	30(1)	60(1)	40(1)	3.5+
40(1)	-	50(1)	40(2)	40(1)	-	50(1)	40(1)	3.0+
40(1)	20(1)	50(1)	40(1)	40(1)	20(1)	40(2)	40(1)	3.0+
40(2)	20(2)	40(2)	30(2)	40(2)	20(2)	50(1)	30(2)	3.5+
40(1)	20(1)	60(1)	50(1)	40(1)	20(1)	60(1)	50(1)	3.0+
31±3.7	23±3.0	47±2.6	40±2.1	34±3.7	23±3.0	44±3.7	40±2.1	111.2±4.0

Table 2. Data from 10ml Placebo Rabbits  
% Horn Involved

Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
30(1)	20(1)	50(2)	30(1)	30(1)	20(1)	40(2)	30(1)	2.5+
50(2)	50(2)	60(1)	30(2)	50(2)	50(2)	60(1)	30(2)	3.5+
40(2)	-	50(1)	20(2)	40(2)	-	50(1)	20(2)	3.0+
20(1)	-	30(1)	20(1)	20(1)	-	30(1)	20(2)	1.5+
-	30(2)	40(1)	40(2)	-	30(2)	40(1)	40(2)	2.5+
50(1)	20(1)	40(2)	30(1)	50(1)	20(1)	50(1)	30(1)	3.0+
30(2)	-	20(2)	40(2)	30(2)	-	20(2)	40(2)	3.0+
30(2)	-	30(2)	40(1)	30(2)	-	50(2)	40(1)	3.0+
50(2)	-	40(1)	50(2)	50(2)	-	40(1)	50(2)	3.0+
30(2)	20(2)	30(1)	40(1)	30(2)	20(2)	50(1)	40(1)	2.5+
33±5.0	14±5.4	39±3.9	34±3.0	33±5.0	14±5.4	43±3.7	34±3.1	100.7±7.5

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Table 3. Data from 75ml Placebo Rabbits  
% Horn Involved

Right Horn					Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall	
40(2)	30(2)	50(2)	40(2)	40(20)	30(2)	40(3)	40(2)	3.5+	
-	-	50(1)	20(1)	-	-	40(1)	20(1)	2.5+	
-	40(2)	30(10)	40(2)	-	40(2)	40(2)	40(2)	3.0+	
40(1)	20(1)	50(1)	20(1)	40(1)	20(1)	50(1)	20(1)	3.0+	
20(1)	-	40(1)	20(1)	20(1)	-	30(1)	20(1)	2.0+	
-	10(1)	20(1)	40(1)	-	10(1)	40(1)	40(1)	2.0+	
-	30.2	50(2)	40(2)	-	30(2)	50(2)	40(2)	3.0+	
40(1)	20(1)	50(1)	20(1)	40(1)	20(1)	30(1)	20(1)	2.5+	
20(1)	-	60(1)	50(1)	20(1)	-	50(1)	50(1)	3.0+	
20(2)	10(1)	40(1)	30(1)	20(2)	10(1)	50(2)	30(1)	3.0+	
18±5.5	16±4.5	44±3.7	32±3.6	18±5.5	16±4.5	42±7.9	32±3.6	100.5±6.8	

Table 4. Data from 10ml 7.5% Icodextrin Rabbits  
% Horn Involved

Right Horn					Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall	
30(1)	20(1)	50(1)	40(1)	30(1)	20(1)	50(1)	40(1)	2.5+	
40(1)	30(1)	50(1)	40(2)	40(1)	30(1)	50(1)	40(2)	3.0+	
40(1)	10(1)	30(1)	10(1)	40(1)	10(1)	10(1)	10(1)	2.0+	
30(1)	20(1)	30(2)	30(1)	30(1)	20(1)	30(2)	30(1)	2.5+	
-	-	10(1)	10(1)	-	-	10(1)	10(1)	1.0+	
40(2)	20(1)	50(1)	30(1)	40(2)	20(1)	50(2)	30(1)	3.5+	
-	10(1)	40(1)	40(2)	-	10(1)	50(1)	40(2)	2.5+	
-	30(2)	30(1)	40(2)	-	30(2)	50(2)	40(2)	3.0+	
30(2)	-	50(1)	30(1)	30(2)	-	40(1)	30(1)	2.5+	
30(2)	-	10(1)	30(1)	30(2)	-	50(1)	30(1)	2.5+	
24±5.4	14±3.7	35±5.0	30±3.7	24±5.4	14±3.7	39±5.3	30±3.7	88.8±9.3*	

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Table 5. Data from 15ml 7.5% Icodextrin Rabbits  
% Horn Involved

Table 6. Data from 25ml 7.5% Icodextrin Rabbits  
% Horn Involved

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Table 7. Data from 50ml 7.5% Icodextrin Rabbits  
% Horn Involved

Table 8. Data from 75ml 7.5% Icodextrin Rabbits  
% Horn Involved

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Table 9. Data from 10ml 20% Icodextrin Rabbits  
% Horn Involved

Right Horn				Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall
20(2)	-	50(2)	30(2)	20(2)	-	50(2)	30(2)	3.0+
10(1)	-	10(1)	10(1)	10(1)	-	50(1)	10(1)	2.0+
40(1)	-	50(2)	30(1)	40(1)	-	40(1)	30(1)	2.5+
40(1)	20(1)	40(1)	30(2)	40(1)	20(1)	30(1)	30(2)	2.5+
-	20(1)	10(1)	-	-	20(1)	20(1)	-	1.0+
30(2)	-	40(1)	30(1)	30(2)	-	30(1)	30(1)	2.5+
30(1)	20(2)	40(1)	40(1)	30(1)	20(2)	10(1)	40(1)	2.5+
10(1)	-	50(1)	20(1)	10(1)	-	30(1)	20(1)	2.0+
20(1)	10(1)	40(1)	40(1)	20(1)	10(1)	30(1)	40(1)	2.5+
20(1)	-	20(1)	20(1)	20(1)	-	40(2)	20(1)	2.0+
22±4.2	7±3.0	35±5.0	25±4.0	22±4.2	7±3.0	33±4.0	25±4.0	78±7.9
*	*	*	*		*		*	*

Table 10. Data from 15ml 20% Icodextrin Rabbits  
% Horn Involved

Right Horn					Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall	
-	-	50(1)	50(1)	-	-	50(1)	50(1)	2.5+	
20(1)	20(1)	20(1)	20(1)	20(1)	20(1)	20(1)	20(1)	2.0+	
-	30(2)	50(1)	30(1)	-	30(2)	20(1)	30(1)	2.5+	
20(1)	20(1)	40(1)	30(1)	20(1)	20(1)	40(1)	30(1)	2.0+	
30(1)	20(1)	40(1)	20(1)	30(1)	20(1)	40(1)	20(1)	2.0+	
40(2)	30(2)	50(1)	50(1)	40(2)	30(2)	50(1)	50(1)	3.0+	
20(1)	-	20(1)	-	-	-	-	-	0.5+	
-	-	-	10(1)	-	-	-	10(1)	0.5+	
-	20(1)	10(1)	10(1)	-	20(1)	20(1)	10(1)	1.5+	
30(1)	30(1)	40(1)	40(1)	20(1)	30(1)	40(1)	30(1)	2.5+	
16±4.8	17±4.0	32±5.7	25±5.2	14±5.0	17±4.0	28±5.9	25±5.2	61.3±11.6	
*			*	*			*	*	

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Table 11. Data from 25ml 20% Icodextrin Rabbits  
% Horn Involved

Table 12. Data from 50ml 20% Icodextrin Rabbits  
% Horn Involved

Right Horn					Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall	
-	-	10(1)	-	-	-	-	-	0.5+	
10(1)	-	10(1)	-	-	-	20(2)	-	1.0+	
20(1)	-	20(1)	10(1)	20(1)	-	10(1)	10(1)	1.5+	
-	10(1)	-	-	-	-	-	-	0.5+	
-	-	10(1)	10(1)	-	-	20(1)	10(1)	1.0+	
30(1)	-	20(1)	10(1)	30(1)	-	20(1)	10(1)	1.5+	
-	10(1)	-	10(1)	-	10(1)	20(1)	10(1)	1.5+	
-	20(1)	40(1)	30(1)	-	20(1)	10(1)	30(1)	2.0+	
-	30(1)	40(1)	10(1)	-	30(1)	20(1)	10(1)	2.0+	
-	30(2)	30(1)	20(1)	-	30(2)	30(2)	20(1)	2.0+	
6±3.4	10±3.9	18±4.7	10±3.0	5±3.4	9±4.1	15±3.1	10±3.0	38.4±7.6	
	*	*		*	*	*	*	*	

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Table 13. Data from 75ml 20% Icodextrin Rabbits  
% Horn Involved

Right Horn					Left Horn				
Bowel	Bladder	Itself	Left	Bowel	Bladder	Itself	Right	Overall	
-	-	10(1)	10(1)	-	-	20(2)	10(1)	1.0+	
-	-	-	-	-	-	30(1)	-	0.5+	
-	-	30(1)	10(1)	-	-	30(1)	10(1)	1.0+	
20(1)	40(1)	10(1)	-	20(1)	40(1)	10(1)	-	2.0+	
-	10(1)	30(1)	10(1)	-	10(1)	30(1)	10(1)	1.5+	
10(1)	10(1)	20(1)	30(1)	10(1)	10(1)	20(1)	30(1)	1.5+	
-	30(1)	10(1)	10(1)	-	30(1)	10(1)	10(1)	1.5+	
-	-	40(1)	10(1)	-	-	20(1)	10(1)	1.5+	
-	-	10(1)	20(1)	-	-	-	20(1)	1.0+	
-	-	10(1)	-	20(1)	-	-	-	0.5+	
3±2.1	9±4.5	17±4.0	10±3.0	5±2.7	9±4.6	17±3.7	10±3.0	31.7±6.3	
*	*	*	*	*	*	*	*	*	

Table 14. Incidence of Adhesion Formation

	# Sites Free/ # Possible	% Adhesion Free	p Value	
			Control	Placebo
Control	2/80	2.5		
10ml Placebo	12/80	15.0	0.012	
75ml Placebo	14/80	17.5	0.004	
10ml 7.5% Icodextrin	12/80	15.0	0.012	1.00
15ml 7.5% Icodextrin	6/80	7.5	0.277	0.211
25ml 7.5% Icodextrin	31/80	38.8	0.000	0.001
50ml 7.5% Icodextrin	32/80	40.0	0.000	0.003
75ml 7.5% Icodextrin	44/80	55.0	0.000	0.000
10ml 20% Icodextrin	16/80	20.0	0.001	0.533
15ml 20% Icodextrin	20/80	25.0	0.000	0.167
25ml 20% Icodextrin	34/80	42.5	0.000	0.000
50ml 20% Icodextrin	36/80	45.0	0.000	0.000
75ml 20% Icodextrin	36/80	45.0	0.000	0.000

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01306

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61L A61K C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 815 879 A (JOHNSON & JOHNSON MEDICAL) 7 January 1998 (1998-01-07)  page 3, line 43 - line 53 claims 1,2,11,12,22 ---	1-8,11, 19,21, 36-39
X	US 5 587 175 A (HENRY RAYMOND L ET AL) 24 December 1996 (1996-12-24)  abstract column 1, line 11 - line 15 column 6, line 24 - line 47 column 7, line 30 - line 35 --- -/--	1-8,11, 14,22, 36-39

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

"T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

2 September 1999

15/09/1999

## Name and mailing address of the ISA

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01306

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 40168 A (UNIV SOUTHERN CALIFORNIA) 19 December 1996 (1996-12-19)  abstract claims 1-23 -----	1, 2, 7, 8, 12, 17, 18, 36-39
A	US 5 093 319 A (HIGHAM PAUL A ET AL) 3 March 1992 (1992-03-03)  column 2, line 19 - line 61 column 2, line 67 - column 3, line 44 -----	1, 2, 12, 13, 22, 36-39

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/01306

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/ GB 99/01306

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.1

Although claims 23-35,38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box 1.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 99 01306

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 23-35,38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

---

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PL1/GB 99/01306

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
EP 0815879	A 07-01-1998	AU 2754097	A	22-01-1998	
		BR 9703773	A	10-11-1998	
		CA 2208939	A	28-12-1997	
		CN 1181980	A	20-05-1998	
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		AU 5956996	A	30-12-1996	
		CA 2223573	A	19-12-1996	
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		AU 612085	A	27-06-1991	
		CA 2028709	A	01-05-1991	
		DE 69015775	D	16-02-1995	
		DE 69015775	T	11-05-1995	
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		EP 0426368	A	08-05-1991	
		ES 2066152	T	01-03-1995	
		GR 3015095	T	31-05-1995	
		IE 64988	B	20-09-1995	
		JP 2056343	C	23-05-1996	
		JP 3167201	A	19-07-1991	
		JP 7090041	B	04-10-1995	

PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Harrison Goddard Foote  
Belmont House  
20 Wood Lane  
LEEDS LS6 2AE  
GRANDE BRETAGNE

11.JUL.2000 032135

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year)	06:07.2000
-------------------------------------	------------

Applicant's or agent's file reference:  
LPB/P15375WO

IMPORTANT NOTIFICATION

International application No. PCT/GB99/01306	International filing date (day/month/year) 13/05/1999	Priority date (day/month/year) 13/05/1998
---	--	--

Applicant

ML LABORATORIES PLC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

**4. REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
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## PATENT COOPERATION TREATY

PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>LPB/P15375W0</b>	<b>FOR FURTHER ACTION</b>	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. <b>PCT/GB 99/ 01306</b>	International filing date (day/month/year) <b>13/05/1999</b>	(Earliest) Priority Date (day/month/year) <b>13/05/1998</b>
Applicant <b>ML LABORATORIES PLC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  **Certain claims were found unsearchable (See Box I).**

3.  **Unity of invention is lacking (see Box II).**

4. With regard to the **title**,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

**DEXTRIN-CONTAINING COMPOSITION FOR PREVENTING SURGICAL ADHESIONS**

5. With regard to the **abstract**,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

—

None of the figures.

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/01306

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: -  
because they relate to subject matter not required to be searched by this Authority, namely:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.1

Although claims 23-35, 38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box 1.1

Rule 39.1(iv) PCT – Method for treatment of the human or animal on the alleged effects of the compound/composition.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 23-35,38 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

-----

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01306

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61L A61K C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 815 879 A (JOHNSON & JOHNSON MEDICAL) 7 January 1998 (1998-01-07)  page 3, line 43 - line 53 claims 1,2,11,12,22 ---	1-8,11, 19,21, 36-39
X	US 5 587 175 A (HENRY RAYMOND L ET AL) 24 December 1996 (1996-12-24)  abstract column 1, line 11 - line 15 column 6, line 24 - line 47 column 7, line 30 - line 35 --- -/-	1-8,11, 14,22, 36-39

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 September 1999

Date of mailing of the international search report

15/09/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Menidjel, R

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01306

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 40168 A (UNIV SOUTHERN CALIFORNIA) 19 December 1996 (1996-12-19)  abstract claims 1-23 ---	1,2,7,8, 12,17, 18,36-39
A	US 5 093 319 A (HIGHAM PAUL A ET AL) 3 March 1992 (1992-03-03)  column 2, line 19 - line 61 column 2, line 67 - column 3, line 44 -----	1,2,12, 13,22, 36-39

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/01306

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0815879	A	07-01-1998	AU 2754097 A		22-01-1998
			BR 9703773 A		10-11-1998
			CA 2208939 A		28-12-1997
			CN 1181980 A		20-05-1998
			JP 10066723 A		10-03-1998
US 5587175	A	24-12-1996	US 5318780 A		07-06-1994
WO 9640168	A	19-12-1996	US 5807833 A		15-09-1998
			AU 5956996 A		30-12-1996
			CA 2223573 A		19-12-1996
			EP 0831856 A		01-04-1998
US 5093319	A	03-03-1992	AT 116555 T		15-01-1995
			AU 612085 A		27-06-1991
			CA 2028709 A		01-05-1991
			DE 69015775 D		16-02-1995
			DE 69015775 T		11-05-1995
			DK 426368 T		13-03-1995
			EP 0426368 A		08-05-1991
			ES 2066152 T		01-03-1995
			GR 3015095 T		31-05-1995
			IE 64988 B		20-09-1995
			JP 2056343 C		23-05-1996
			JP 3167201 A		19-07-1991
			JP 7090041 B		04-10-1995

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# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum) LPB/P15375WO

### Box No. I TITLE OF INVENTION

PREVENTION OF SURGICAL ADHESIONS

### Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ML Laboratories Plc  
Blaby Hall  
Church Street  
BLABY  
LE8 4FA  
United Kingdom

This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (that is, country) of nationality:  
GB

State (that is, country) of residence:  
GB

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box for the purposes of:

### Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

BROWN, Colin  
ML Laboratories Plc  
Blaby Hall  
Church Street  
BLABY  
LE8 4FA  
United Kingdom

This person is:

applicant only

applicant and inventor

inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
GB

State (that is, country) of residence:  
GB

This person is applicant  all designated States  all designated States except the United States of America  the United States of America only  the States indicated in the Supplemental Box for the purposes of:

Further applicants and/or (further) inventors are indicated on a continuation sheet.

### Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:  agent  common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Harrison Goddard Foote  
Belmont House  
20 Wood Lane  
LEEDS  
LS6 2AE United Kingdom (GB)

Telephone No.

+44 113 2258262

Facsimile No.

+44 113 2304702

Teleprinter No.

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

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**Box No.V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

**Regional Patent**

- AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> AL Albania .....                               | <input checked="" type="checkbox"/> LS Lesotho .....                                   |
| <input checked="" type="checkbox"/> AM Armenia .....                               | <input checked="" type="checkbox"/> LT Lithuania .....                                 |
| <input checked="" type="checkbox"/> AT Austria .....                               | <input checked="" type="checkbox"/> LU Luxembourg .....                                |
| <input checked="" type="checkbox"/> AU Australia .....                             | <input checked="" type="checkbox"/> LV Latvia .....                                    |
| <input checked="" type="checkbox"/> AZ Azerbaijan .....                            | <input checked="" type="checkbox"/> MD Republic of Moldova .....                       |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina .....                | <input checked="" type="checkbox"/> MG Madagascar .....                                |
| <input checked="" type="checkbox"/> BB Barbados .....                              | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia ..... |
| <input checked="" type="checkbox"/> BG Bulgaria .....                              | <input checked="" type="checkbox"/> MN Mongolia .....                                  |
| <input checked="" type="checkbox"/> BR Brazil .....                                | <input checked="" type="checkbox"/> MW Malawi .....                                    |
| <input checked="" type="checkbox"/> BY Belarus .....                               | <input checked="" type="checkbox"/> MX Mexico .....                                    |
| <input checked="" type="checkbox"/> CA Canada .....                                | <input checked="" type="checkbox"/> NO Norway .....                                    |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein .....  | <input checked="" type="checkbox"/> NZ New Zealand .....                               |
| <input checked="" type="checkbox"/> CN China .....                                 | <input checked="" type="checkbox"/> PL Poland .....                                    |
| <input checked="" type="checkbox"/> CU Cuba .....                                  | <input checked="" type="checkbox"/> PT Portugal .....                                  |
| <input checked="" type="checkbox"/> CZ Czech Republic .....                        | <input checked="" type="checkbox"/> RO Romania .....                                   |
| <input checked="" type="checkbox"/> DE Germany .....                               | <input checked="" type="checkbox"/> RU Russian Federation .....                        |
| <input checked="" type="checkbox"/> DK Denmark .....                               | <input checked="" type="checkbox"/> SD Sudan .....                                     |
| <input checked="" type="checkbox"/> EE Estonia .....                               | <input checked="" type="checkbox"/> SE Sweden .....                                    |
| <input checked="" type="checkbox"/> ES Spain .....                                 | <input checked="" type="checkbox"/> SG Singapore .....                                 |
| <input checked="" type="checkbox"/> FI Finland .....                               | <input checked="" type="checkbox"/> SI Slovenia .....                                  |
| <input checked="" type="checkbox"/> GB United Kingdom .....                        | <input checked="" type="checkbox"/> SK Slovakia .....                                  |
| <input checked="" type="checkbox"/> GD Grenada .....                               | <input checked="" type="checkbox"/> SL Sierra Leone .....                              |
| <input checked="" type="checkbox"/> GE Georgia .....                               | <input checked="" type="checkbox"/> TJ Tajikistan .....                                |
| <input checked="" type="checkbox"/> GH Ghana .....                                 | <input checked="" type="checkbox"/> TM Turkmenistan .....                              |
| <input checked="" type="checkbox"/> GM Gambia .....                                | <input checked="" type="checkbox"/> TR Turkey .....                                    |
| <input checked="" type="checkbox"/> HR Croatia .....                               | <input checked="" type="checkbox"/> TT Trinidad and Tobago .....                       |
| <input checked="" type="checkbox"/> HU Hungary .....                               | <input checked="" type="checkbox"/> UA Ukraine .....                                   |
| <input checked="" type="checkbox"/> ID Indonesia .....                             | <input checked="" type="checkbox"/> UG Uganda .....                                    |
| <input checked="" type="checkbox"/> IL Israel .....                                | <input checked="" type="checkbox"/> US United States of America .....                  |
| <input checked="" type="checkbox"/> IN India .....                                 | <input checked="" type="checkbox"/> UZ Uzbekistan .....                                |
| <input checked="" type="checkbox"/> IS Iceland .....                               | <input checked="" type="checkbox"/> VN Viet Nam .....                                  |
| <input checked="" type="checkbox"/> JP Japan .....                                 | <input checked="" type="checkbox"/> YU Yugoslavia .....                                |
| <input checked="" type="checkbox"/> KE Kenya .....                                 | <input checked="" type="checkbox"/> ZW Zimbabwe .....                                  |
| <input checked="" type="checkbox"/> KG Kyrgyzstan .....                            |  |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea ..... |  |
| <input checked="" type="checkbox"/> KR Republic of Korea .....                     |  |
| <input checked="" type="checkbox"/> KZ Kazakhstan .....                            |  |
| <input checked="" type="checkbox"/> LC Saint Lucia .....                           | <input checked="" type="checkbox"/> SOUTH AFRICA (ZA) .....                            |
| <input checked="" type="checkbox"/> LK Sri Lanka .....                             | <input checked="" type="checkbox"/> UNITED ARAB EMIRATES (AE) .....                    |
| <input checked="" type="checkbox"/> LR Liberia .....                               | <input type="checkbox"/>   |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- SOUTH AFRICA (ZA) .....
- UNITED ARAB EMIRATES (AE) .....
- 

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

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Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 13 May 1998	9810127.2	GB	GB	
item (2) 19 March 1999	09/272,713	US	US	
item (3)				

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s):

\* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

#### Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):		
ISA /	Date (day/month/year)	Number	Country (or regional Office)

#### Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:	This international application is accompanied by the item(s) marked below:
request : 3	1. <input checked="" type="checkbox"/> fee calculation sheet
description (excluding sequence listing part) : 10	2. <input type="checkbox"/> separate signed power of attorney
claims : 5	3. <input type="checkbox"/> copy of general power of attorney; reference number, if any:
abstract : 1	4. <input type="checkbox"/> statement explaining lack of signature
drawings : 7	5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s):
sequence listing part of description :	6. <input type="checkbox"/> translation of international application into (language):
Total number of sheets : 26	7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material
	8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form
	9. <input type="checkbox"/> other (specify):
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: GB

#### Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

HARRISON GODDARD FOOTE

Harrison Goddard Foote (WB)

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only
Date of receipt of the record copy by the International Bureau:

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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LPB/P15375WO	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/01306	International filing date (day/month/year) 13/05/1999	Priority date (day/month/year) 13/05/1998
International Patent Classification (IPC) or national classification and IPC A61L31/00		
<p style="text-align: right;">11.JUL.2000*032136</p> <p>Applicant ML LABORATORIES PLC. et al.</p>		
<p>1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 11 sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I    <input checked="" type="checkbox"/> Basis of the report</li> <li>II    <input type="checkbox"/> Priority</li> <li>III    <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV    <input type="checkbox"/> Lack of unity of invention</li> <li>V    <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI    <input type="checkbox"/> Certain documents cited</li> <li>VII    <input type="checkbox"/> Certain defects in the international application</li> <li>VIII    <input type="checkbox"/> Certain observations on the international application</li> </ul>		

Date of submission of the demand 10/12/1999	Date of completion of this report 06.07.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Deck, A  Telephone No. +49 89 2399 8432



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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01306

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1,8-10	as originally filed		
2-7	as received on	22/06/2000 with letter of	22/06/2000

**Claims, No.:**

1-39	as received on	22/06/2000 with letter of	22/06/2000
------	----------------	---------------------------	------------

**Drawings, sheets:**

1/7-7/7	as originally filed
---------	---------------------

2. The amendments have resulted in the cancellation of:

the description,      pages:  
 the claims,      Nos.:  
 the drawings,      sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.  
 claims Nos. 23-35, 38.

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01306

because:

- the said international application, or the said claims Nos. 23-35, 38 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 1-39
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-39
	No:	Claims
Industrial applicability (IA)	Yes:	Claims see separate sheet
	No:	Claims

**2. Citations and explanations**

**see separate sheet**

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**Concerning section III:**

Claims 23-35 and 38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Concerning section V:**

The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: EP-A-0 815 879 (JOHNSON & JOHNSON MEDICAL) 7 January 1998 (1998-01-07)  
D2: US-A-5 587 175 (HENRY RAYMOND L ET AL) 24 December 1996 (1996-12-24)

**1. Novelty, inventive step**

D1 describes the use of a bioabsorbable material comprising an oxidized polymer, e.g. oxidized dextrin, although only oxidized methylcellulose is exemplified, for limiting surgical adhesions. This material is not described as containing more than 15% of polymers with a degree of polymerisation greater than 12. The material of D1 therefore does not fulfill the requirement of maintaining the volume of the solution placed in the body cavity, whereas the aqueous composition of the present invention is an osmotic agent which maintains the volume of the solution placed in the body cavity.

D2 discloses aqueous compositions which can be equally hyperosmotic, hypoosmotic or isoosmotic, comprising a polymer, e.g. cyclodextrin, polydextrin, maltodextrin, i.e. a polymer with no particular requirement regarding the degree of polymerisation. These compositions are applied on the cornea, and are not meant to be used in a body cavity as claimed in the present invention. Moreover, the composition of the invention has to be osmotic and to comprise polymers with a degree of polymerisation greater than 12, in order to achieve the maintenance of the volume of the solution placed in the body

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/01306

cavity.

The technical effect achieved by the osmotic agent of the invention is to increase the surface of protection against adhesions in a body cavity. The prior art available only describes the protection of particular areas or organs by covering them with films or sponges comprising compositions of polysaccharides. It would not have been obvious for the skilled person that a composition comprising dextrin wherein the degree of polymerisation is greater than 12 and being osmotic would achieve this technical effect over the prior art.

Therefore, the present application meets the requirements of Article 33 (2) and (3) PCT.

**2. Industrial applicability**

For the assessment of the present claims 23-35 and 38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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PCT/CB99/01306

DESC

proteoglycans, or the glycosaminoglycan moieties of proteoglycans, including dermatan sulfate, chondroitin sulfate, keratan sulfate, heparan sulfate, heparin and alginate.

By attempting to inhibit fibroblast invasion, the approach of WO 92/21354 is one of post-adhesion treatment since fibroblast invasion is a later stage, that is to say, it occurs after formation of the adhesion. The invention of WO 92/21354 attempts to prevent the adhesion becoming permanent. By contrast the present invention is concerned with the prevention of the occurrence of an adhesion.

According to a first aspect of the present invention there is provided a method of preventing or reducing the incidence of adhesions in or associated with a body cavity comprising an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

The term "dextrin" means a glucose polymer which is produced by the hydrolysis of starch and which consists of glucose units linked together by means mainly of  $\alpha$ -1,4 linkages. Typically dextrans are produced by the hydrolysis of starch obtained from various natural products such as wheat, rice, maize and tapioca. In addition to  $\alpha$ -1,4 linkages, there may be a proportion of  $\alpha$ -1,6 linkages in a particular dextrin, the amount depending on the starch starting material. Since the rate of biodegradability of  $\alpha$ -1,6 linkages is typically less than that for  $\alpha$ -1,4 linkages, it is preferred that, for many applications, the percentage of  $\alpha$ -1,6 linkages is less than 10% and more preferably less than 5%.

Any dextrin is a mixture of polyglucose molecules of different chain lengths. As a result no single number can adequately characterise the molecular weight of such a polymer. Accordingly, various averages are used, the most common being the weight average molecular weight ( $M_w$ ) and the number average molecular weight ( $M_n$ ).  $M_w$  is particularly sensitive to changes in the high molecular weight content

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of a polymer whilst Mn is largely influenced by changes in the low molecular weight content of the polymer.

It is preferred that the Mn of the dextrin is in the range of from 1,000 to 30,000 and 5 ideally the Mw is in the range of from 3,000 to 50,000. More preferably, the Mn is from 3,000 to 8,000 and the Mw is from 5,000 to 50,000.

The term "degree of polymerisation" (DP) can also be used in connection with polymer mixtures. For a single polymer molecule, DP means the number of polymer 10 units. For a mixture of molecules of different DP's, weight average DP and number average DP correspond to Mw and Mn. In addition, DP can also be used to characterise a polymer by referring to the polymer mixture having a certain percentage of polymers of DP greater than a particular number or less than a particular number.

15

It is preferred that the dextrin contains more than 15% of polymers of DP greater than 12 and, more preferably, more than 50% of polymers of DP greater than 12.

The dextrin used in the present invention is water soluble or at least forms a solution 20 in water or a gel formulation. The dextrin used in this invention may be in the form of either unsubstituted dextrin (as obtained by the hydrolysis of starch) or may be substituted by one or more different groups. The substituents may be negatively charged groups, for instance, sulfate groups, neutral groups, or positively charged groups, for instance, quaternary ammonium groups. In the case where the substituent 25 group is sulfate, it is preferred that the sulfated polysaccharide contains at least one sulfate group per saccharide (glucose) unit.

The present invention also provides a composition for preventing or reducing the incidence of adhesions in or associated with a body cavity comprising an aqueous 30 formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce such adhesions, wherein the dextrin contains more than 15% of polymers

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with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.

- 5 The present invention further provides the use of a composition for preventing or reducing the incidence of adhesions in or associated with a body cavity comprising an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.
- 10

( The present invention further provides the use of the polysaccharide dextrin in the manufacture of a composition comprising an aqueous solution or gel formulation of dextrin for preventing or reducing adhesions in humans and animals.

15 Dextrin is a useful material for the production of an adhesion-preventing composition because, *inter alia*, it is non-toxic, cheap and has the ability to hold fluid in a body cavity. It is also readily metabolised within the body.

20

Preferably, a composition of the invention is applied to the appropriate body cavity or area after the operation has been carried out.

( 25

Preferably, the composition of the present invention is allowed to remain in the body cavity for a minimum of 2 to 3 days and especially over the period during which fibrin exudation is at a maximum. More preferably, the composition should remain in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).

30

Preferably, a composition of the invention should be applied to the body cavity in a volume large enough to keep the surfaces apart. For the peritoneum, the volume should preferably be in the range 500-2000 ml and, more preferably, about 1000 ml-1500 ml.

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Preferably, the composition should be applied to the appropriate body cavity or area in differing concentrations ideally over a concentration range of 2.5-18% and more ideally over a concentration range of 3-5% and most ideally at about 4% by weight, said concentration range is selected for a specified time span, even more ideally the concentration range is selectively altered over a period of time.

5 Preferably, the composition should include a concentration of dextrin which is such that the fluid largely holds in place over the period it resides in the cavity. Where a composition includes 4% by weight of dextrin then a suitable dwell period for one infusion might be of the order of 2 to 3 days. A high concentration is liable to cause 10 ingress of fluid. A second infusion at day 3 may extend the total dwell period from 6 to 7 days.

( 15 Alternatively, a composition having a dextrin concentration of from 12 to 15% by weight may be used in a smaller volume (perhaps about 750 ml) and will be subject to ingress of fluid. However a single infusion might be sufficient for the full 6 to 7 day period.

Comparing dextrin with dextran, the latter has relatively poor biocompatibility. It is 20 subject to immunological hypersensitivity due to its concentration in lymph nodes and its lack of metabolisability. At best, a dextran solution or suspension will act not so much to separate surfaces and therefore prevent adhesions but simply as a lubricant. Dextrin advantageously serves as an osmotic agent, which can maintain the volume of a solution in the peritoneal cavity. The continued presence of the 25 dextrin solution within the cavity serves to separate tissues which otherwise may adhere to each other.

The use of a solution or gel formulation of dextrin is also advantageous by comparison with a prior art technique which makes use of synthetic films in the form 30 of patches which are applied to particular areas where maximum damage has occurred. However, in the case of a body cavity, such as the peritoneum, the damage is liable to occur as well at a distance from the operative site, especially in

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laparoscopy, due to the drying which takes place. In some instances global damage over an area of as much as two square metres can take place.

In responding to a wound, the body causes circulating fibrinogen to form fibrin and it  
5 is this production of fibrin which is associated with the formation of adhesions. Calcium ions are required to polymerise fibrinogen to fibrin and, accordingly, a composition of the present invention may include a calcium binding agent such as EDTA or sodium citrate.

10 A composition of the present invention may include a suitable lubricant such as a phospholipid.

( A composition of the present invention may include a hyaluronate or glycocosaminoglycan or a material which is associated with serosal lubrication and  
15 which has strong anti-adhesive properties. In this case the dextrin solution or gel formulation is effective in spreading the hyaluronate throughout the whole peritoneum.

20 A composition of the present invention may include an antibiotic agent or a material/agent which is associated with preventing an infection or build up of bacteria or foreign bodies or the like. A composition including such a material/agent would be particularly advantageous in prevention or amelioration of pelvic inflammatory disease.

25 A composition of the present invention may also include a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate and/or methylene blue.

30 The present invention provides a preferred composition comprising an aqueous solution or gel formulation of dextrin, one or more phospholipids and

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hyaluronate. Such a composition is not only highly effective in preventing adhesions but also has a good shelf life.

Mesothelial secretion of prostacyclin has been demonstrated and this activity  
5 enhances the non-stick properties of the mesothelium. The present invention provides a composition comprising dextrin together with prostacyclin or an analogue thereof.

According to a further aspect of the invention there is provided a biocompatible, bioresorbable, and non-toxic adhesion prevention kit for surgical use in humans or  
10 animals, comprising an aqueous solution or gel formulation of dextrin as hereinbefore described, and optionally or additionally comprising a calcium binding agent as hereinbefore described and/or a suitable lubricant as hereinbefore described and/or prostacyclin or an analogue thereof as hereinbefore described and/or an antibiotic agent as hereinbefore described..

15

### EVIDENCE IN SUPPORT OF THE INVENTION

#### PROTOCOL:

Animals: One hundred thirty, female New Zealand White rabbits, 2.4-2.7 kg, were purchased from Irish Farms (Norco, CA) and quarantined in the USC Vivaria for at least 2 days prior to use. Ten rabbits were randomised into thirteen treatment groups prior to initiation of surgery. The rabbits were housed on a 12:12 light:dark cycle with food and water available *ad libitum*.

25 Materials: The solutions (7.5% [wt/vol] icodextrin-Lot # 98A06G33, 20% [wt/vol] icodextrin-Batch # SP184772 and placebo (electrolyte solution for icodextrin)-Batch # SP184829 were supplied by ML Laboratories Plc. Icodextrin is a [1 → 4] - α - Glucan having more than 85% of its molecules with molecular weights between 1,640 - 45,000 with a weight average molecular weight of approximately 20,000. The placebo electrolyte solution contained 5.4g sodium chloride, 4.5g sodium lactate, 257 mg calcium chloride, 51 mg magnesium chloride in 1 litre water for injection. The sutures used to close the muscle and skin were 3-0 coated Dexon II suture (Davis and Geck, Manati, PR).

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**Amended Claims**

1. A composition for preventing or reducing the incidence of adhesions in or associated with a body cavity comprising an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.  
10
2. A composition according to Claim 1 wherein the aqueous formulation is a solution.
3. A composition according to Claim 1 wherein the aqueous formulation is a gel.  
15
4. A composition according to any preceding claim wherein the percentage of  $\alpha$ -1,6 linkages in the dextrin is less than 10%.
- 20 5. A composition according to Claim 4 wherein the percentage of  $\alpha$ -1,6 linkages in the dextrin is less than 5%.
6. A composition according to any preceding claim wherein the number average molecular weight (Mn) of the dextrin is in the range 1,000 to 30,000.  
25
7. A composition according to Claim 6 wherein the Mn of the dextrin is in the range 3,000 to 8,000.
8. A composition according to any preceding claim wherein the weight average molecular weight (Mw) of the dextrin is in the range 3,000 to 50,000.  
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9. A composition according to Claim 8 wherein the Mw of the dextrin is from 5,000 to 50,000.

10. A composition according to any of Claims 1-9 wherein the dextrin contains 5 more than 50% of polymers with a degree of polymerisation (DP) greater than 12.

11. A composition according to any preceding claim wherein the dextrin is unsubstituted dextrin.

10 12. A composition according to any of Claims 1-10 wherein the dextrin is substituted by one or more different groups selected from the group consisting of negatively charged groups, sulfate groups, neutral groups, positively charged groups and quaternary ammonium groups.

15 13. A composition according to Claim 12 wherein the dextrin is sulfated dextrin containing at least one sulfate group per saccharide (glucose) unit.

20 14. A composition according to any preceding claim in which the dextrin is present in an amount of from 2.5-18 % by weight of the composition.

15. A composition according to Claim 14 in which the dextrin is present in an amount of from 3-5 % by weight of the composition.

25 16. A composition according to either of Claims 14 or 15 in which the dextrin is present in an amount of about 4 % by weight of the composition.

17. A composition according to any preceding claim which further includes a calcium binding agent.

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18. A composition according to Claim 17 wherein the calcium binding agent is either EDTA or sodium citrate.
19. A composition according to any preceding claim which further includes a  
5 suitable lubricant.
20. A composition according to Claim 19 wherein the lubricant is a phospholipid.
21. A composition according to any preceding claim which further includes a  
10 hyaluronate.
22. A composition according to any preceding claim which further includes a compound selected from one or more of the following compounds, glycosolaminoglycan, an antibiotic agent, prostacyclin or an analogue thereof,  
15 a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate and/or methylene blue.
23. A method of preventing or reducing the incidence of adhesions in or associated with a body cavity, which comprises introducing into the body  
20 cavity an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce the incidence of such adhesions, wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate  
25 tissues which otherwise may adhere to each other.
24. A method according to Claim 23 wherein the aqueous formulation is a solution.
- 30 25. A method according to Claim 23 wherein the aqueous formulation is a gel.

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26. A method according to any of Claims 23-25 wherein said composition is applied to the appropriate body cavity after a surgical operation has been carried out.

5 27. A method according to any of Claims 23-26 wherein the composition is allowed to remain in the body cavity for a minimum of 2 to 3 days.

10 28. A method according to any of Claims 23-27 wherein the composition is allowed to remain in the body cavity over the period during which fibrin exudation is at a maximum.

15 29. A method according to any of Claims 23-28 wherein the composition remains in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).

30. A method according to any of Claims 23-29 wherein the composition is applied to the peritoneal cavity in a volume in the range 500-2000 ml.

20 31. A method according to Claim 30 wherein the composition is applied to the peritoneal cavity in a volume in the range 1000 ml-1500 ml.

32. A method according to any of Claims 23-31 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 2.5-18 % by weight of the composition.

25 33. A method according to Claim 32 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 3-5 % by weight of the composition.

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34. A method according to either Claims 32 or 33 wherein the dextrin is applied to the appropriate body cavity in an amount of about 4 % by weight of the composition.
- 5 35. A method according to any of Claims 23-34 wherein the concentration range of the dextrin is selectively altered over a period of time.
- 10 36. A biocompatible, bioresorbable, and non-toxic adhesion prevention kit for surgical use in humans or animals, comprising an aqueous formulation of dextrin.
37. A kit according to Claim 36 wherein the aqueous formulation is either a solution or a gel.
- 15 38. Use of a composition according to Claim 1 and optionally including any one or more of the features of Claims 2-22 for preventing or reducing the incidence of adhesions in or associated with a body cavity which comprises introducing into the body cavity an aqueous formulation containing the polysaccharide dextrin wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.
- 20
- 25 39. Products containing an aqueous formulation of the polysaccharide dextrin and any one or more of the features of Claims 17-22 as a combined preparation for use in preventing or reducing the incidence of adhesions in or associated with a body cavity wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12 and acts as an osmotic agent to maintain a volume of the aqueous formulation in the body cavity serving to separate tissues which otherwise may adhere to each other.
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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference  LPB/P15375WO	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No.  PCT/GB99/01306	International filing date (day/month/year)  13/05/1999	Priority date (day/month/year)  13/05/1998
International Patent Classification (IPC) or national classification and IPC  A61L31/00		
<p><b>Applicant</b>  ML LABORATORIES PLC. et al.</p> <p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 11 sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I   <input checked="" type="checkbox"/> Basis of the report</li> <li>II   <input type="checkbox"/> Priority</li> <li>III   <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV   <input type="checkbox"/> Lack of unity of invention</li> <li>V   <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI   <input type="checkbox"/> Certain documents cited</li> <li>VII   <input type="checkbox"/> Certain defects in the international application</li> <li>VIII   <input type="checkbox"/> Certain observations on the international application</li> </ul>		

Date of submission of the demand  10/12/1999	Date of completion of this report  06.07.2000
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Deck, A  Telephone No. +49 89 2399 8432



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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/01306

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1,8-10	as originally filed		
2-7	as received on	22/06/2000 with letter of	22/06/2000

**Claims, No.:**

1-39	as received on	22/06/2000 with letter of	22/06/2000
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**Drawings, sheets:**

1/7-7/7	as originally filed
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2. The amendments have resulted in the cancellation of:

the description,      pages:  
 the claims,      Nos.:  
 the drawings,      sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.  
 claims Nos. 23-35, 38.

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# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01306

because:

- the said international application, or the said claims Nos. 23-35, 38 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. .

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims 1-39
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-39
	No:	Claims
Industrial applicability (IA)	Yes:	Claims see separate sheet
	No:	Claims

### 2. Citations and explanations

**see separate sheet**

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**Concerning section III:**

Claims 23-35 and 38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Concerning section V:**

The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

- D1: EP-A-0 815 879 (JOHNSON & JOHNSON MEDICAL) 7 January 1998 (1998-01-07)  
D2: US-A-5 587 175 (HENRY RAYMOND L ET AL) 24 December 1996 (1996-12-24)

**1. Novelty, inventive step**

D1 describes the use of a bioabsorbable material comprising an oxidized polymer, *e.g.* oxidized dextrin, although only oxidized methylcellulose is exemplified, for limiting surgical adhesions. This material is not described as containing more than 15% of polymers with a degree of polymerisation greater than 12. The material of D1 therefore does not fulfill the requirement of maintaining the volume of the solution placed in the body cavity, whereas the aqueous composition of the present invention is an osmotic agent which maintains the volume of the solution placed in the body cavity.

D2 discloses aqueous compositions which can be equally hyperosmotic, hypoosmotic or isoosmotic, comprising a polymer, *e.g.* cyclodextrin, polydextrin, maltodextrin, *i.e.* a polymer with no particular requirement regarding the degree of polymerisation. These compositions are applied on the cornea, and are not meant to be used in a body cavity as claimed in the present invention. Moreover, the composition of the invention has to be osmotic and to comprise polymers with a degree of polymerisation greater than 12, in order to achieve the maintenance of the volume of the solution placed in the body

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**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB99/01306

cavity.

The technical effect achieved by the osmotic agent of the invention is to increase the surface of protection against adhesions in a body cavity. The prior art available only describes the protection of particular areas or organs by covering them with films or sponges comprising compositions of polysaccharides. It would not have been obvious for the skilled person that a composition comprising dextrin wherein the degree of polymerisation is greater than 12 and being osmotic would achieve this technical effect over the prior art.

Therefore, the present application meets the requirements of Article 33 (2) and (3) PCT.

**2. Industrial applicability**

For the assessment of the present claims 23-35 and 38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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proteoglycans, or the glycosaminoglycan moieties of proteoglycans, including dermatan sulfate, chondroitin sulfate, keratan sulfate, heparan sulfate, heparin and alginate.

- 5 By attempting to inhibit fibroblast invasion, the approach of WO 92/21354 is one of post-adhesion treatment since fibroblast invasion is a later stage, that is to say, it occurs after formation of the adhesion. The invention of WO 92/21354 attempts to prevent the adhesion becoming permanent. By contrast the present invention is concerned with the prevention of the occurrence of an adhesion.

10

According to a first aspect of the present invention there is provided a method of preventing or reducing the incidence of post-operative adhesions in or associated with a body cavity, which comprises introducing into the body cavity an aqueous solution or suspension or gel formulation containing the polysaccharide dextrin.

15

The term "dextrin" means a glucose polymer which is produced by the hydrolysis of starch and which consists of glucose units linked together by means mainly of  $\alpha$ -1,4 linkages. Typically dextrans are produced by the hydrolysis of starch obtained from various natural products such as wheat, rice, maize and tapioca. In addition to  $\alpha$ -1,4 linkages, there may be a proportion of  $\alpha$ -1,6 linkages in a particular dextrin, the amount depending on the starch starting material. Since the rate of biodegradability of  $\alpha$ -1,6 linkages is typically less than that for  $\alpha$ -1,4 linkages, it is preferred that, for many applications, the percentage of  $\alpha$ -1,6 linkages is less than 10% and more preferably less than 5%.

25

Any dextrin is a mixture of polyglucose molecules of different chain lengths. As a result no single number can adequately characterise the molecular weight of such a polymer. Accordingly, various averages are used, the most common being the weight average molecular weight ( $M_w$ ) and the number average molecular weight ( $M_n$ ).  $M_w$  is particularly sensitive to changes in the high molecular weight content

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of a polymer whilst Mn is largely influenced by changes in the low molecular weight content of the polymer.

It is preferred that the Mn of the dextrin is in the range of from 1,000 to 30,000 and 5 ideally the Mw is in the range of from 3,000 to 50,000. More preferably, the Mn is from 3,000 to 8,000 and the Mw is from 5,000 to 50,000.

The term "degree of polymerisation" (DP) can also be used in connection with polymer mixtures. For a single polymer molecule, DP means the number of polymer 10 units. For a mixture of molecules of different DP's, weight average DP and number average DP correspond to Mw and Mn. In addition, DP can also be used to characterise a polymer by referring to the polymer mixture having a certain percentage of polymers of DP greater than a particular number or less than a particular number.

15

It is preferred that the dextrin contains more than 15% of polymers of DP greater than 12 and, more preferably, more than 50% of polymers of DP greater than 12.

The dextrin used in the present invention is water soluble or at least forms a 20 suspension in water or a gel formulation. The dextrin used in this invention may be in the form of either unsubstituted dextrin (as obtained by the hydrolysis of starch) or may be substituted by one or more different groups. The substituents may be negatively charged groups, for instance, sulfate groups, neutral groups, or positively charged groups, for instance, quaternary ammonium groups. In the case where the 25 substituent group is sulfate, it is preferred that the sulfated polysaccharide contains at least one sulfate group per saccharide (glucose) unit.

The present invention also provides a composition comprising an aqueous solution or suspension or gel formulation of the polysaccharide dextrin in which the amount of 30 dextrin is effective to prevent or reduce the incidence of post-operative adhesions.

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ART 34 AMDT

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The present invention further provides the use of a composition in the prevention or reduction of the incidence of post-operative adhesions, the composition comprising a aqueous solution or suspension or gel formulation of the polysaccharide dextrin.

- 5     The present invention further provides the use of the polysaccharide dextrin in the manufacture of a composition comprising an aqueous solution or suspension or gel formulation of dextrin for preventing or reducing post-operative adhesions in humans and animals.
- 10    Dextrin is a useful material for the production of an adhesion-preventing composition because, *inter alia*, it is non-toxic, cheap and has the ability to hold fluid in a body cavity. It is also readily metabolised within the body.

Preferably, a composition of the invention is applied to the appropriate body cavity or area after the operation has been carried out.
- 15    Preferably, the composition of the present invention is allowed to remain in the body cavity for a minimum of 2 to 3 days and especially over the period during which fibrin exudation is at a maximum. More preferably, the composition should remain 20 in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).
- 25    Preferably, a composition of the invention should be applied to the body cavity in a volume large enough to keep the surfaces apart. For the peritoneum, the volume should preferably be in the range 500-2000 ml and, more preferably, about 1000 ml-1500 ml.
- 30    Preferably, the composition should be applied to the appropriate body cavity or area in differing concentrations ideally over a concentration range of 2.5-18% and more ideally over a concentration range of 3-5% and most ideally at about 4% by weight,

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said concentration range is selected for a specified time span, even more ideally the concentration range is selectively altered over a period of time.

Preferably, the composition should include a concentration of dextrin which is such  
5 that the fluid largely holds in place over the period it resides in the cavity. Where a composition includes 4% by weight of dextrin then a suitable dwell period for one infusion might be of the order of 2 to 3 days. A high concentration is liable to cause ingress of fluid. A second infusion at day 3 may extend the total dwell period from 6 to 7 days.

10

Alternatively, a composition having a dextrin concentration of from 12 to 15% by weight may be used in a smaller volume (perhaps about 750 ml) and will be subject to ingress of fluid. However a single infusion might be sufficient for the full 6 to 7 day period.

15

Comparing dextrin with dextran, the latter has relatively poor biocompatibility. It is subject to immunological hypersensitivity due to its concentration in lymph nodes and its lack of metabolisability. At best, a dextran solution or suspension will act not so much to separate surfaces and therefore prevent adhesions but simply as a lubricant. Dextrin advantageously serves as an osmotic agent, which can maintain the volume of a solution in the peritoneal cavity. The continued presence of the dextrin solution within the cavity serves to separate tissues which otherwise may adhere to each other.

20  
25 The use of a solution or suspension or gel formulation of dextrin is also advantageous by comparison with a prior art technique which makes use of synthetic films in the form of patches which are applied to particular areas where maximum damage has occurred. However, in the case of a body cavity, such as the peritoneum, the damage is liable to occur as well at a distance from the operative site, especially in  
30 laparoscopy, due to the drying which takes place. In some instances global damage over an area of as much as two square metres can take place.

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In responding to a wound, the body causes circulating fibrinogen to form fibrin and it is this production of fibrin which is associated with the formation of adhesions. Calcium ions are required to polymerise fibrinogen to fibrin and, accordingly, a composition of the present invention may include a calcium binding agent such as  
5 EDTA or sodium citrate.

- A composition of the present invention may include a suitable lubricant such as a phospholipid.  
10 A composition of the present invention may include a hyaluronate or glycocosolaminoglycan, a material which is associated with serosal lubrication and which has strong anti-adhesive properties. In this case the dextrin solution or suspension or gel formulation is effective in spreading the hyaluronate throughout the whole peritoneum.  
15  
A composition of the present invention may include an antibiotic agent or a material/agent which is associated with preventing an infection or build up of bacteria or foreign bodies or the like. A composition including such a material/agent would be particularly advantageous in prevention or amelioration of pelvic  
20 inflammatory disease.

- A composition of the present invention may also include a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate and/or methylene blue.  
25 The present invention provides a preferred composition comprising an aqueous solution or suspension or gel formulation of dextrin, one or more phospholipids and hyaluronate. Such a composition is not only highly effective in preventing adhesions but also has a good shelf life.

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Mesothelial secretion of prostacyclin has been demonstrated and this activity enhances the non-stick properties of the mesothelium. The present invention provides a composition comprising dextrin together with prostacyclin or an analogue thereof.

- 5 According to a second aspect of the invention there is provided a biocompatible, bioresorbable, and non-toxic post-operative adhesion prevention kit for surgical use in humans or animals, comprising an aqueous solution or suspension or gel formulation of dextrin as hereinbefore described, and optionally or additionally comprising a calcium binding agent as hereinbefore described and/or a suitable lubricant as hereinbefore described and/or prostacyclin or an analogue thereof as hereinbefore described and/or an antibiotic agent as hereinbefore described..
- 10

#### EVIDENCE IN SUPPORT OF THE INVENTION

15 PROTOCOL:

Animals: One hundred thirty, female New Zealand White rabbits, 2.4-2.7 kg, were purchased from Irish Farms (Norco, CA) and quarantined in the USC Vivaria for at least 2 days prior to use. Ten rabbits were randomised into thirteen treatment groups prior to initiation of surgery. The rabbits were housed on a 12:12 light:dark cycle with food and water available *ad libitum*.

Materials: The solutions (7.5% [wt/vol] icodextrin-Lot # 98A06G33, 20% [wt/vol] icodextrin-Batch # SP184772 and placebo (electrolyte solution for icodextrin)-Batch # SP184829 were supplied by ML Laboratories Plc. Icodextrin is a [1 → 4] - α - Glucan having more than 85% of its molecules with molecular weights between 1,640 - 45,000 with a weight average molecular weight of approximately 20,000. The placebo electrolyte solution contained 5.4g sodium chloride, 4.5g sodium lactate, 257 mg calcium chloride, 51 mg magnesium chloride in 1 litre water for injection. The sutures used to close the muscle and skin were 3-0 coated Dexon II suture (Davis and Geck, Manati, PR).

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## CLAIMS

1. A composition comprising an aqueous formulation containing the polysaccharide dextrin in an amount effective to prevent or reduce the incidence of post-operative adhesions in or associated with a body cavity.  
5
2. A composition according to Claim 1 wherein the aqueous formulation is a solution, suspension or a gel.
- 10 3. A composition according to either preceding claim wherein the percentage of  $\alpha$ -1,6 linkages in dextrin is less than 10%.
4. A composition according to Claim 3 wherein the percentage of  $\alpha$ -1,6 linkages in dextrin is less than 5%.
- 15 5. A composition according to any preceding claim wherein the number average molecular weight ( $M_n$ ) of dextrin is in the range 1,000 to 30,000.
6. A composition according to Claim 5 wherein the  $M_n$  of dextrin is in the range  
20 3,000 to 8,000.
7. A composition according to any preceding claim wherein the weight average molecular weight ( $M_w$ ) of dextrin is in the range 3,000 to 50,000.
- 25 8. A composition according to Claim 7 wherein the  $M_w$  of dextrin is from 5,000 to 50,000.
9. A composition according to any preceding claim wherein the dextrin contains  
30 more than 15% of polymers with a degree of polymerisation (DP) greater than 12.

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10. A composition according to any of Claims 1-8 wherein the dextrin contains more than 50% of polymers with a degree of polymerisation (DP) greater than 12.
- 5 11. A composition according to any preceding claim wherein the dextrin is unsubstituted dextrin.
12. A composition according to any of Claims 1-10 wherein the dextrin is substituted by one or more different groups selected from the group consisting of negatively charged groups, sulfate groups, neutral groups, 10 positively charged groups and quaternary ammonium groups.
13. A composition according to Claim 12 wherein the dextrin is sulfated dextrin containing at least one sulfate group per saccharide (glucose) unit.
- 15 14. A composition according to any preceding claim in which the dextrin is present in an amount of from 2.5-18 % by weight.
15. A composition according to Claim 14 in which the dextrin is present in an 20 amount of from 3-5 % by weight.
16. A composition according to either of Claims 14 or 15 in which the dextrin is present in an amount of about 4 % by weight.
- 25 17. A composition according to any preceding claim which further includes a calcium binding agent.
18. A composition according to Claim 17 wherein the calcium binding agent is either EDTA or sodium citrate.

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19. A composition according to any preceding claim which further includes a suitable lubricant.
20. A composition according to Claim 19 wherein the lubricant is a phospholipid.  
5
21. A composition according to any preceding claim which further includes a hyaluronate.
22. A composition according to any preceding claim which further includes a compound selected from one or more of the following compounds, glycosolaminoglycan, an antibiotic agent, prostacyclin or an analogue thereof, a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate and/or methylene blue.  
10
- 15 23. A method of preventing or reducing the incidence of post-operative adhesions in or associated with a body cavity, which comprises introducing into the body cavity an aqueous formulation containing the polysaccharide dextrin.
24. A method according to Claim 23 wherein the aqueous formulation is selected  
20 from the group consisting of a solution, a suspension and a gel.
25. A method according to either Claim 23 or 24 wherein said composition is applied to the appropriate body cavity after the operation has been carried out.
- 25 26. A method according to any of Claims 23-25 wherein the composition is allowed to remain in the body cavity for a minimum of 2 to 3 days.
27. A method according to any of Claims 23-26 wherein the composition is allowed to remain in the body cavity over the period during which fibrin exudation is at a maximum.  
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28. A method according to any of Claims 23-27 wherein the composition remains in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).
- 5 29. A method according to any of Claims 23-28 wherein the composition is applied to the body cavity in a volume large enough to keep tissue surfaces apart.
- 10 30. A method according to any of Claims 23-29 wherein the volume of the composition applied to the peritoneum is in the range 500-2000 ml.
31. A method according to Claim 30 wherein the volume of the composition applied to the peritoneum is in the range 1000 ml-1500 ml.
- 15 32. A method according to any of Claims 23-31 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 2.5-18 % by weight.
- 20 33. A method according to Claim 32 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 3-5 % by weight.
34. A method according to either Claims 32 or 33 wherein the dextrin is applied to the appropriate body cavity in an amount of about 4 % by weight.
- 25 35. A method according to any of Claims 23-34 wherein the concentration range of dextrin is selectively altered over a period of time.
- 30 36. A biocompatible, bioresorbable, and non-toxic post-operative adhesion prevention kit for surgical use in humans or animals, comprising an aqueous formulation of dextrin.

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37. A kit according to Claim 36 wherein the aqueous formulation is selected from the group consisting of a solution, a suspension and a gel.
- 5       38. Use of a composition according to Claim 1 and optionally including any one or more of the features of Claims 2-22 for preventing or reducing the incidence of post-operative adhesions in or associated with a body cavity which comprises introducing into the body cavity an aqueous formulation containing the polysaccharide dextrin.
- 10      39. Products containing an aqueous formulation of the polysaccharide dextrin and any one or more of the features of Claims 17-22 as a combined preparation for use in preventing or reducing the incidence of post-operative adhesions in or associated with a body cavity.

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